

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 December 2000 (28.12.2000)

PCT

(10) International Publication Number
WO 00/78355 A2

- (51) International Patent Classification⁷: **A61K 47/48**
- (21) International Application Number: **PCT/GB00/02216**
- (22) International Filing Date: 19 June 2000 (19.06.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9914187.1 18 June 1999 (18.06.1999) GB
9930252.3 22 December 1999 (22.12.1999) GB
- (71) Applicant (*for all designated States except US*): **ML LABORATORIES** [GB/GB]; 17 Hanover Square, London W1R 9AJ (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **DUNCAN, Ruth** [GB/GB]; School of Pharmacy, University of London, 29/39 Brunswick Square, London, WC1N 1AX (GB). **HRECZUK-HIRST, Dale** [GB/GB]; School of Pharmacy, University of London, 29/39 Brunswick Square, London, WC1N 1AX (GB). **GERMAN, Lisa** [GB/GB]; School of Pharmacy, University of London, 29/39 Brunswick Square, London, WC1N 1AX (GB).
- (74) Agent: **HARRISON GODDARD FOOTE**; Tower House, Merrion Way, Leeds LS2 8PA (GB).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— *Without international search report and to be republished upon receipt of that report.*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 00/78355 A2

(54) Title: **BIOLOGICALLY ACTIVE MATERIALS**

(57) Abstract: The invention relates to a polymer drug conjugate for the treatment of cancer comprising a succinoylated dextrin wherein said succinoylation enhances the *in vivo* stability of said conjugate.

BIOLOGICALLY ACTIVE MATERIALS

Field of Invention

5 This invention relates to biologically active materials and, in particular, to materials which comprise a biodegradable polymer linked to a biologically active agent. The invention is concerned with materials known as polymer-drug conjugates which typically contain a therapeutic agent for instance, a bioactive cytotoxic drug, linked to a polymer back-bone. The linkage between the polymer and the drug is typically by
10 covalent bonding. However, the invention is applicable to other polymer conjugates including those where the biologically active agent is an imaging agent, such as tyrosinamide, a diagnostic agent, or a targeting agent such as biotin.

Reference will be made hereinbelow to polymer-drug conjugates in which the drugs
15 are anticancer agents. However, the present invention has application in connection with other drugs and/or bioactive agents.

Background of the Invention

20 In designing a polymer-drug conjugate, the aim is to deliver a drug effectively to a therapeutic site such as a tumour. It is known, for instance, that polymer-drugs given intravenously can accumulate selectively in solid tumour tissue by the EPR effect.

The most commonly used anticancer agents are low molecular weight compounds
25 which readily gain access to cells by rapid passage across the cell membrane. After intravenous (IV) administration, a large percentage of the injected dose leaves the circulation within a few minutes, resulting in a ubiquitous body distribution of drug and little selective concentration in tumour tissue. By creating a macromolecular polymer-anticancer drug conjugate, there is provided an opportunity to improve
30 tumour specific targeting, to minimise drug entry into sites of toxicity, to control precisely the rate of drug liberation at the target site (giving opportunities for long-

term controlled release) and to deliver the active principal intracellularly, thereby providing a means to overcome p-glycoprotein related multidrug resistance.

5 Numerous polymers have been proposed for synthesis of polymer-drug conjugates including polyaminoacids, polysaccharides such as dextran, and synthetic polymers such as N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer. However, these polymers have limitations. For example, a dextran-doxorubicin conjugate has been tested clinically and been found to be much more toxic than the parent drug. Furthermore the HPMA copolymers which have been clinically tested have the
10 disadvantage of being non-biodegradable in the main chain.

WO-A-98/56424 discloses a polymer-drug conjugate in which the polymer is the polysaccharide dextrin. Such a polymer-drug conjugate may be prepared in various ways. One method involves succinoylating dextrin and reacting the succinoylated
15 dextrin with the drug or a reactive derivative thereof.

WO-A-98/56424 includes an example in which the extent of succinoylation of dextrin varies from 2.26 to 6.64 Mol%. In a further example the drug doxorubicin is conjugated to succinoylated dextrans in which the extent of succinoylation varies
20 from 0.5 to 14.9 Mol%.

WO-A-98/56424 also includes examples showing the rate of degradation of dextrin both in the absence and in the presence of appropriate enzymes and also in rat plasma.
25

For at least certain applications the rate of degradation of dextrin in a dextrin-drug conjugate is an important consideration. For instance, it may be desirable to have a relatively slow rate of degradation in some applications while in other applications a faster rate of degradation is either acceptable or indeed even preferred.
30

Statement of Invention

It has now been surprisingly discovered that the rate of dextrin degradation is highly dependent on the degree of dextrin backbone substitution. As a result, it is possible
5 to tailor the dextrin by appropriate substitution of its backbone in order to achieve a desired rate of degradation.

According to a first aspect of the invention there is provided a polymer drug conjugate comprising:

- 10 i) at least one anti-cancer drug; and
ii) a dextrin polymer

characterised in that said dextrin polymer is modified by the addition of pendent groups so that the stability of the polymer drug conjugate is enhanced.

15 The term "dextrin" means a glucose polymer which is produced by the hydrolysis of starch and which consists of glucose units linked together by means mainly of alpha-1,4 linkages. Typically dextrins are produced by the hydrolysis of starch obtained from various natural products such as wheat, rice, maize and tapioca. In addition to
20 alpha-1,4 linkages, there may be a proportion of alpha-1,6 linkages in a particular dextrin, the amount depending on the starch starting material. Since the rate of biodegradability of alpha-1,6 linkages is typically less than that for alpha-1,4 linkages, for many applications it is preferred that the percentage of alpha-1,6 linkages is less than 10% and more preferably less than 5%.

25 Any dextrin is a mixture of polyglucose molecules of different chain lengths. As a result, no single number can adequately characterise the molecular weight of such a polymer. Accordingly various averages are used, the most common being the weight average molecular weight (Mw) and the number average molecular weight (Mn). Mw is particularly sensitive to changes in the high molecular weight content of a
30 polymer whilst Mn is largely influenced by changes in the low molecular weight of the polymer.

It is preferred that the Mw of the dextrin is in the range from 1,000 to 200,000, more preferably from 2,000 to 55,000.

- 5 The term 'degree of polymerisation' (DP) can also be used in connection with polymer mixtures. For a single polymer molecule, DP means the number of polymer units. For a mixture of molecules of different DP's, weight average DP and number average DP correspond to Mw and Mn. In addition DP can also be used to characterise a polymer by referring to the polymer mixture having a certain
10 percentage of polymers of DP greater than a particular number or less than a particular number.

- It is preferred that, in the dextrin-drug conjugate of the present invention, the dextrin contains more than 15 % of polymers of DP greater than 12 and, more preferably,
15 more than 50% of polymers of DP greater than 12.

Modifications to dextrin may be negatively charged groups, neutral groups or positively charged groups, (eg quaternary ammonium groups).

- 20 In a further preferred embodiment of the invention said dextrin modification is succinoylation.

- In a yet further preferred embodiment of the invention said dextrin succinoylation is greater than 20 mol %. Preferably said dextrin succinoylation is at least 30mol%.
25 More preferably still said succinoylation is from 30% to 40%.

More preferably still said succinoylation is 30mol%; 31mol%; 32mol%; 33mol%; 34mol%; 35mol%; 36mol%; 37mol%; 38mol%; 39mol%; 40mol%. Ideally said succinoylation is 34mol%.

In a yet further preferred embodiment of the invention said succinoylated dextrin comprises an anti-cancer agent selected from: cyclophosphamide; melphalan; carmusline; methotrexate, 5-fluorouracil; cytarabine; mercaptopurine; anthracyclines; daunorubicin; doxorubicin; epirubicin; vinca alkaloids; vinblastin; vincristine;
5 dactinomycin; mitomycin C; taxol; L-asparaginase; G-CSF; cisplatin; carboplatin.

More preferably still said anti-cancer agent is doxorubicin.

According to a further aspect of the invention there is provided a pharmaceutical
10 composition comprising a polymer drug conjugate according to any previous aspect or embodiment of the invention.

In a preferred embodiment of the invention said composition comprises a diluent, carrier or excipient.

15

In a further preferred embodiment of the invention said polymer drug conjugate is for use in the manufacture of a medicament for the treatment of cancer.

According to a further aspect of the invention there is provided a method to treat an
20 animal, ideally a human being, suffering from cancer by administration of the polymer drug conjugate according to the invention.

It has been found that, in the case of substitution of the dextrin backbone by succinoylation, relatively rapid degradation takes place at a degree of succinoylation
25 of up to about 15%. By contrast a degree of succinoylation above 30% very markedly reduces the rate of degradation.

The present invention provides a dextrin-drug conjugate in which the degree of substitution of the dextrin chain is greater than 15%, more preferably greater than
30 20% and most preferably greater than 30%.

The drug of the dextrin-drug conjugate may be loaded on the polymer via a linking group, such as succinoyl, in which case it may be attached to some or all of the linking groups. Alternatively the drug may be directly loaded onto the dextrin backbone in which case the drug itself acts as the substituting group. As a further possibility the drug may be loaded partly via a substituting group and partly directly onto the dextrin backbone.

An embodiment of the invention will now be described by example only and with reference to the following tables and figures;

10

Table 1 represents the characteristics of different batches of succinoylated dextrin doxorubicin conjugates;

Table 2 shows the anticancer activity of succinoylated dextrin doxorubicin conjugates;

15

Figure 1 is a graphical representation of the degradation of dextrin, succinoylated dextrin and a succinoylated dextrin doxorubicin conjugate (5% succinoylation, 6% doxorubicin);

20

Figure 2 is a graphical representation of the degradation of hyper-succinoylated dextrin doxorubicin(34% succinoylation) conjugate with time;

Figure 3 is a graphical representation of the preferential accumulation of succinoylated dextrin doxorubicin conjugate compared to an unconjugated control;

25

Figure 4 illustrates the effect of the degree of dextrin succinoylation on biodistribution of ^{125}I -labelled Dextrin at 34mol% after i.v. administration;

Figure 5 illustrates a comparison of the 1 and 34 mol% modified ^{125}I -labelled dextrin at 5 min post i.v administration;

30

Figure 6 illustrates a comparison of the 1 and 34 mol% modified ^{125}I -labelled dextrin at 1hr post i.v administration; and

- 5 Figure 7 represents the presence of ^{125}I -labelled dextrin in the peritoneal wash after i.p. administration at 1hr

Detailed description of the invention

10 *Example 1*

Dextrin (Mw 51,000 Da) was succinoylated using a modification of the method described by Bruneel *et al* (Polymer, 35 (12),(1994), 2656-2658). Doxorubicin was then conjugated directly via an amide bond, conjugated via an N-*cis*-aconityl spacer or conjugated via a glycyI-N-*cis*-aconityl spacer.

15

Polymer degradation (unmodified dextrin, succinoylated dextrin (5, 15 mol %) and conjugate) was measured in the presence of amylase or lysosomal enzymes to monitor either changes in polymer molecular weight (GPC) or doxorubicin release (HPLC).

20

The dextrin-doxorubin conjugates had a doxorubicin loading of 6-12 wt% dependent on the reaction conditions used and the degree of succinylation of the dextrin intermediate. Table 1 shows the characteristics of several batches of dextrin-succ-doxorubicin.

25

Table 1 Characteristics of batches of dextrin-succ-doxorubicin

Batch No	Dox (wt%)	Free Dox (% total Dox)
1	11.7	0.8
2	11.9	2.0
3	8.7	1.2
4	8.4	0.1

30

After a 180 min incubation with amylase, unmodified dextrin is almost completely degraded to low molecular products, whilst the succinoylated dextrin (5 and 15 mol %) and dextrin-succ-doxorubicin show a biphasic pattern of degradation giving rise to fragments of Mw 4,000, 9,500 and 6,400 Da respectively. Unmodified dextrin had a $t_{1/2}$ (time for mass to reach half of its original) of 20 min, succinoylated dextrin and dextrin-succ-doxorubicin a $t_{1/2}$ of approximately 15 min.

Example 2

In this example the degradation of dextrans of different degrees of modification was compared. The results are shown in Figure 1. It will be seen that native dextrin is rapidly degraded as are also dextrin with 5% succinoylation (whether with or without 6% Dox) and dextrin with 15% succinoylation. However, if dextrin is 34% succinoylated the degree of degradation is markedly less, there being zero% reduction of the peak mass of primary peak after 60 minutes and only 20% reduction after 180 minutes. In addition, Figure 2 shows that 34% succinoylated dextrin doxorubicin conjugate is similarly stable over an extended time course when compared to unconjugated or low level succinoylated (5%) controls.

Example 3

In this example increased uptake of 34% succinoylated dextrin-doxorubicin by tumour cells is shown. Male C57 were injected with 10^6 B16F10 murine melanoma cells subcutaneously with either doxorubicin hydrochloride or dextrin-succinoyl-doxorubicin (34 mol % succinoylation, 11.8% doxorubicin) at 5mg/kg doxorubicin equivalence into the intraperitoneal cavity (i.p.).

The mice were then culled after 2, 5, and 30 mins and after 1, 2, 5, 24, and 48 hours. Tumours were removed and weighed. The tumour was then homogenised and doxorubicin extracted and quantified by HPLC for total doxorubicin present, Figure 3.

Figure 3 shows there is approximately a three fold increase in tumour levels of doxorubicin were found for the conjugate for all time intervals from 2 min up to 24 hours. After this period, there is no difference between conjugate or the free drug. The elevated levels of the conjugate were at their highest 5 min after injection.

5

Example 4

In this example the pharmacology of succinolyated dextrin doxorubicin is determined and is presented in Table 2. Twenty four C57 black mice were injected subcutaneously (s.c.) with 10^5 B16F10 murine melanoma cells as described above and then monitored daily for well-being and the presence of palpable tumours. When the tumours were palpable, mice were randomly assigned into groups of six and their tumours measured with a micrometer gauge. Tumour size and mouse body weight is recorded. Each group is then injected intra-peritoneally with either sterile saline (negative control), free doxorubicin (5mg kg^{-1}) in sterile saline or dextrin-doxorubicin (11.8 wt%, 34% succinolyation) at either 5mg kg^{-1} or 10mg kg^{-1} , on days 0,1 and 2. The mice were monitored daily and tumour size and body weight recorded. Once the tumour area exceeded 2.89 cm^2 the mice were culled according to UKCCCR guidelines. Mouse survival is then expressed as % T/C (test/control saline).

20

The animals treated with doxorubicin (5mg kg^{-1}) displayed a drop in body weight consistent with toxicity. However all mice tolerated the dextrin –doxorubicin conjugate at both doses. The higher dose (10mg kg^{-1}) equates to approximately 2 mg of conjugate. As shown in Table 2, dextrin- doxorubicin conjugate resulted in a T/C of approximately 140% indicating anticancer activity. In contrast, free doxorubicin was not active in this experiment.

25

Example 5

30

The tumour model used was B16F10 murine melanoma. Viable tumour cells (10^5) were injected subcutaneously into C57/BL mice near the base of the neck. When

tumours were visible ^{125}I -labelled dextrin (100 μl , 5×10^5 (cpm) was injected i.v. into the tail vein and the mice were culled at 5 min and 1h. A blood sample was taken and the mouse weighed. The major organs were removed and homogenised in a known volume of DI water. Samples (3 x 1ml) of each tissue were taken and assayed
5 radioactivity. The total amount of radioactivity per organ was expressed as the percentage of the injected dose or as percent of the dose injected per gram of organ.

Figure 4 shows the effect of the degree of dextrin succinylation on biodistribution of ^{125}I -labelled Dextrin at 34mol% after i.v. administration. Over time it can be noted
10 that there is an decrease in the overall % recovery of the injected dose. Example of organ recoveries, tumour levels increased from 2.5% dose (5 min) to 7.3% dose (1h). Liver levels increased from 10.8% dose (5min) to 11.5% dose (1h) and spleen levels increased from 5.5% dose (5 min) to 9.7% dose (1h). All of the other organs showed a decrease in the % recovery.

15

Example 6

Figure 5 shows a comparison of the 1 and 34 mol% modified ^{125}I -labelled dextrin at 5 min. At five minutes the overall recovery is greatest in the 34mol%, the tumour %
20 recovery rose from 0.6% dose to 2.5% dose after an increased succinylation and there was over a two fold difference in the other major organs except the kidney where the % recovery dropped from 15.7% to 11.5% of the injected dose.

Example 7

25 Figure 6 shows a comparison of the ^{125}I -labelled dextrin at 1h. At 1h the accumulation in the kidneys is greater than at 1mol% modified dextrin the 34mol% giving 7.3% dose. The overall recovery for both mol% modified dextrin has decreased over time.

30

Example 8

Figures 7 show comparisons of recovery in the i.p. wash in the tumour bearing mice.

The dextrin at 34mol% is being retained in the i.p. cavity for longer than the other

5 modified polymers

10

15

20

25

30

CLAIMS

1. A polymer drug conjugate comprising:
 - i) at least one anti-cancer drug; and
 - 5 ii) a dextrin polymercharacterised in that said dextrin polymer is modified by addition of pendent groups so that the stability of the polymer drug conjugate is enhanced.
2. A polymer drug conjugate according to Claim 1, wherein said modification is
10 by the addition of pendent groups selected from: negatively charged groups, neutral groups or positively charged groups.
3. A polymer drug conjugate according to Claim 1 or 2, wherein said
modification is by the addition of quaternary ammonium groups.
- 15 4. A polymer drug conjugate according to Claims 1 or 2, wherein said dextrin modification is succinylation.
5. A polymer drug conjugate according to Claim 4, wherein said dextrin is
20 succinoylated to at least 20mol%.
6. A polymer drug conjugate according to claim 4, wherein said dextrin is
succinoylated to at least 30mol%.
- 25 7. A polymer drug conjugate according to Claim 6, wherein said dextrin is
succinoylated from 30% to 40mol%.
8. A polymer drug conjugate according to Claim 7, wherein said dextrin is
succinoylated from 32% to 36%.
- 30 9. A polymer drug conjugate according to Claim 8 wherein said dextrin is
succinoylated to about 34mol%.

10. A polymer drug conjugate according to Claims 1 - 9, wherein said anti cancer agent is selected from: cyclophosphamide; melphalan; carmusline; methotrexate, 5-fluorouracil; cytarabine; mercaptopurine; anthracyclines; daunorubicin, doxorubicin; 5
epirubicin; vinca alkaloids; vinblastin; vincristine; dactinomycin; mitomycin C; taxol; L-asparaginase; G-CSF; cisplatin; carboplatin.
11. A pharmaceutical composition comprising a polymer drug conjugate according to any preceding Claims.
- 10
12. A pharmaceutical composition according to Claim 11 wherein said composition comprises a diluent, carrier or excipient.
13. The use of a polymer drug conjugate according to Claims 1 - 9 for the 15
manufacture of a medicament for the treatment of cancer.
14. A method of treatment of an animal subject the method including the administration to the animal a pharmaceutically effective amount of the polymer drug conjugate according to any preceding Claim.

20

25

TABLE 2

Compound	Dose mg kg ⁻¹ (day 0,1,2)	Days survival after treatment (mean ± SD)	T/C (%)	Toxic deaths
Control (saline)	-	4.3 ± 0.5	100	0/6
doxorubicin	5	4.5 ± 0.5 ^{ns}	103	0/6
Dextrin-Dox	5	6.2 ± 0.8 [*]	142	0/6
Dextrin -Dox	10	6.0 ± 1.1 ^{**}	138	0/6

N= 6 ns = not significant * p = 0.0004 ** p = 0.005

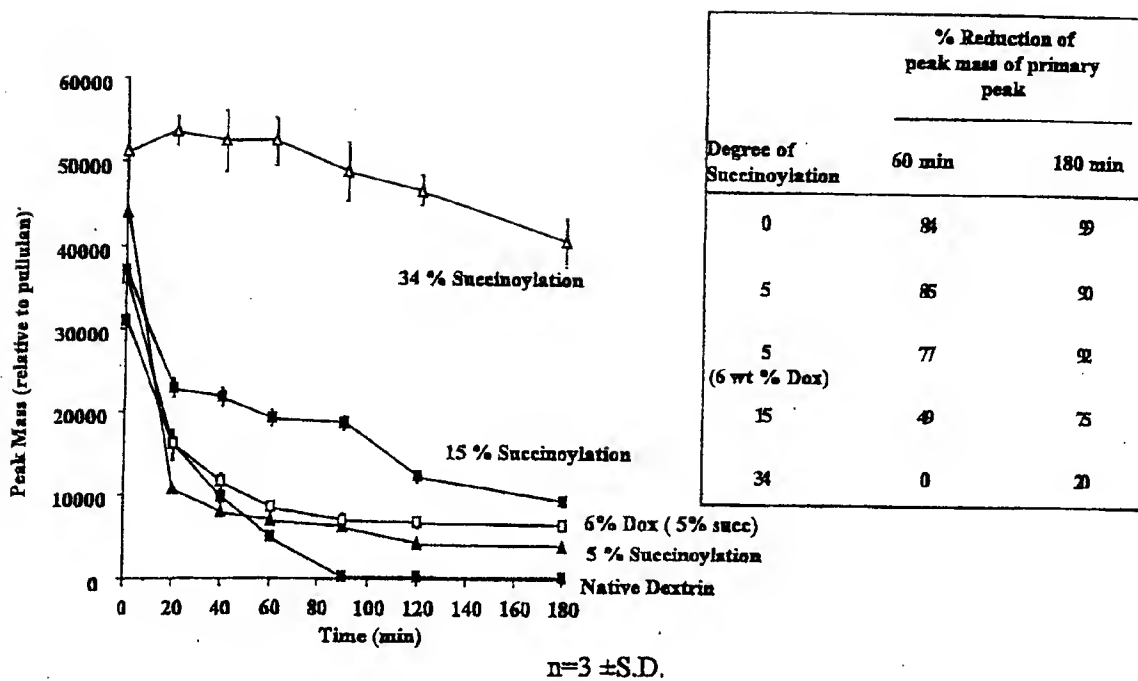


Figure 1 1/6

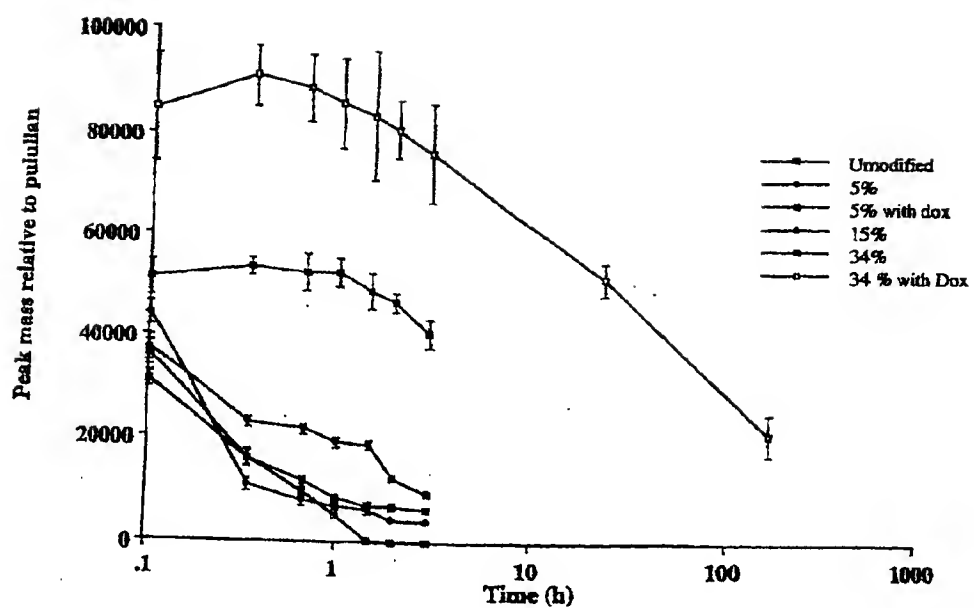


Figure 2 2/6

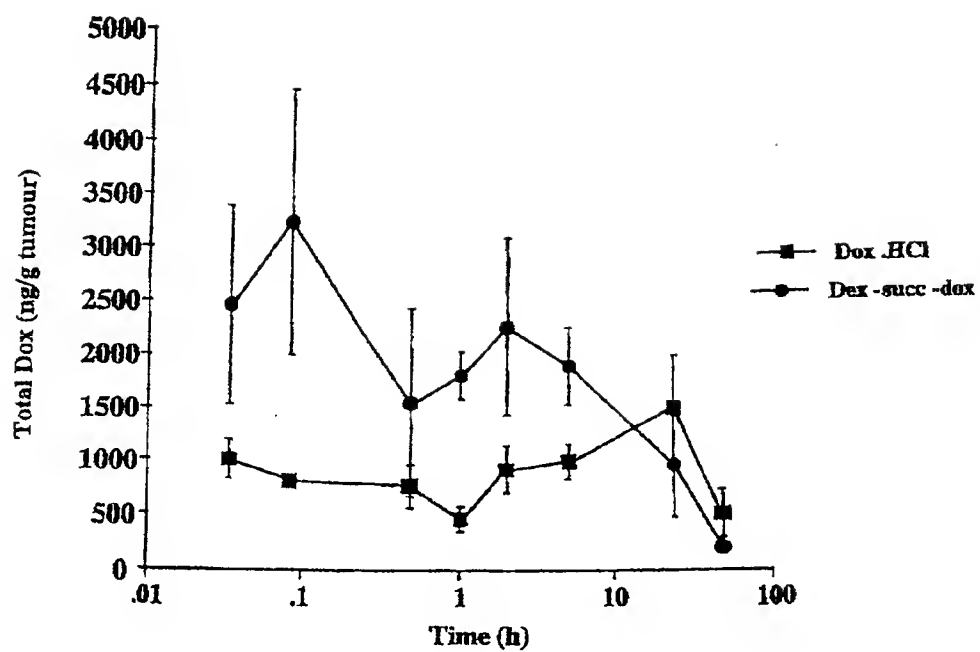
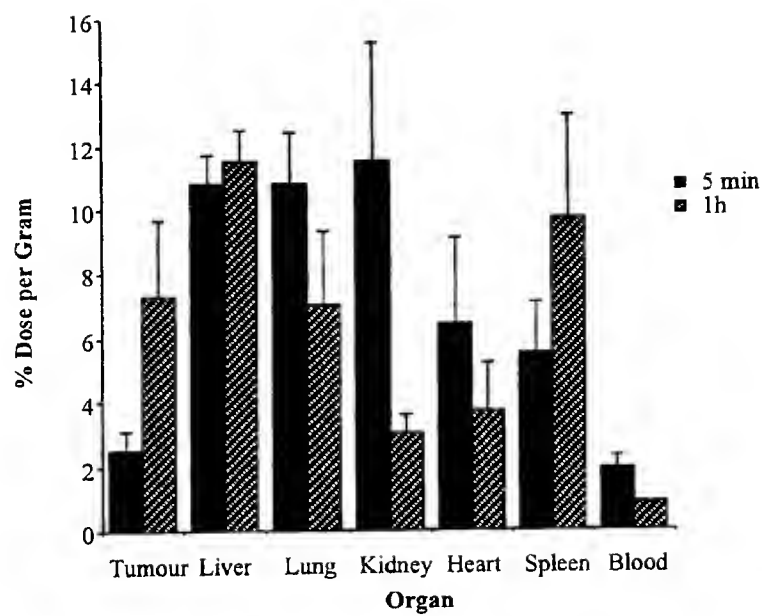


Figure 3 3/6



4/6

Figure 4

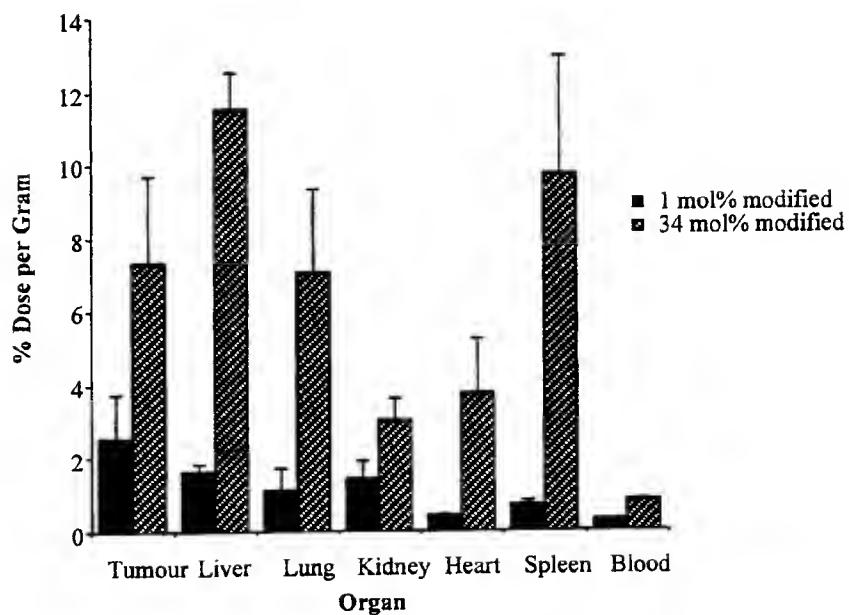
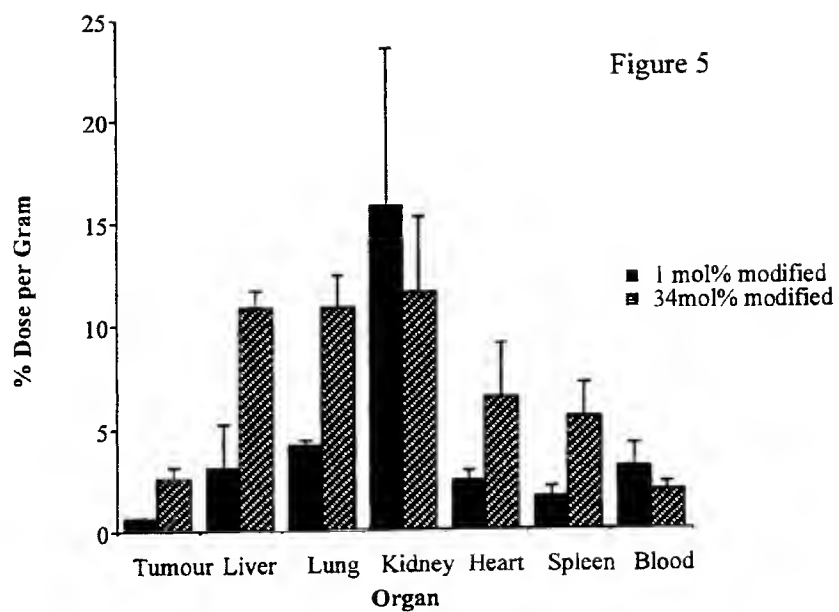


Figure 6

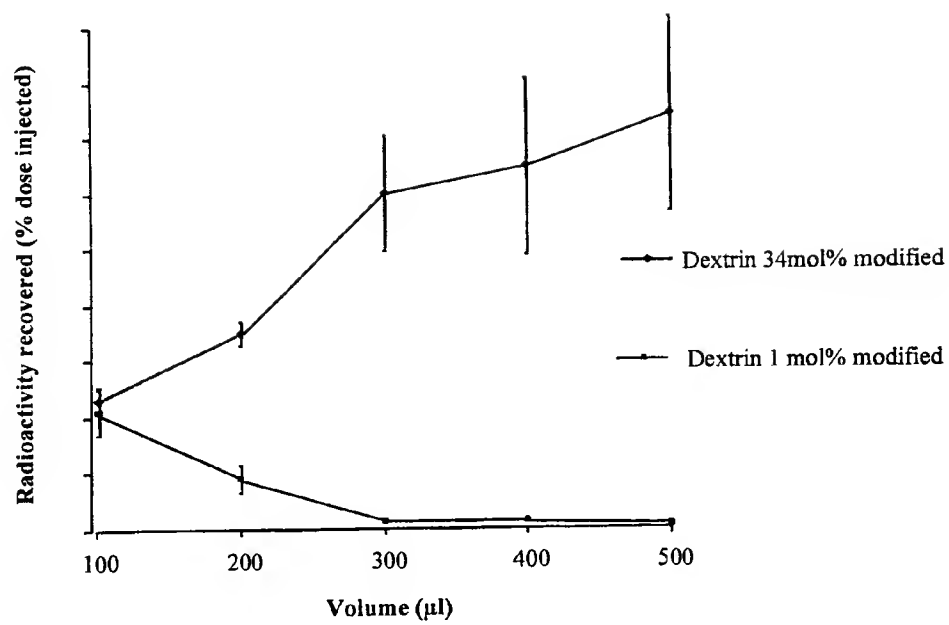


Figure 7.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 December 2000 (28.12.2000)

PCT

(10) International Publication Number
WO 00/78355 A3

- (51) International Patent Classification⁷: **A61K 47/48**, 51/06 // 101:02
- (74) Agent: **HARRISON GODDARD FOOTE**; Tower House, Merrion Way, Leeds LS2 8PA (GB).
- (21) International Application Number: PCT/GB00/02216
- (22) International Filing Date: 19 June 2000 (19.06.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9914187.1 18 June 1999 (18.06.1999) GB
9930252.3 22 December 1999 (22.12.1999) GB
- (71) Applicant (for all designated States except US): **ML LABORATORIES PLC** [GB/GB]; 17 Hanover Square, London W1R 9AJ (GB).
- (72) Inventors: and
- (75) Inventors/Applicants (for US only): **DUNCAN, Ruth** [GB/GB]; School of Pharmacy, University of London, 29/39 Brunswick Square, London, WC1N 1AX (GB). **IIRECZUK-HIRST, Dale** [GB/GB]; School of Pharmacy, University of London, 29/39 Brunswick Square, London, WC1N 1AX (GB). **GERMAN, Lisa** [GB/GB]; School of Pharmacy, University of London, 29/39 Brunswick Square, London, WC1N 1AX (GB).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
with international search report
- (88) Date of publication of the international search report:
21 February 2002
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/78355 A3

(54) Title: BIOLOGICALLY ACTIVE MATERIALS

(57) Abstract: The invention relates to a polymer drug conjugate for the treatment of cancer comprising a succinoylated dextrin wherein said succinoylation enhances the *in vivo* stability of said conjugate.

INTERNATIONAL SEARCH REPORT

national Application No

PCT/GB 00/02216

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61K51/06 //A61K101:02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, PAJ, WPI Data, EPO-Internal, MEDLINE, CANCERLIT, CHEM ABS Data, DISSERTATION ABS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 56424 A (CASSIDY JAMES ;DUNCAN RUTH (GB); GERMAN LISA (GB); HIRST DALE (GB)) 17 December 1998 (1998-12-17) examples 3.1,3.2,4 figures 3A,3B ---	1-14
X	EP 0 477 931 A (MERCIAN CORP) 1 April 1992 (1992-04-01) examples ---	1-14
Y	WO 96 35720 A (KHAN RIAZ ;KONOWICZ A PAUL (GB); FIDIA ADVANCED BIOPOLYMERS SRL (I)) 14 November 1996 (1996-11-14) page 10, line 1 -page 11, line 13 --- -/--	1-14



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents .

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

30 May 2001

Date of mailing of the international search report

08/06/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Dullaart, A

INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 00/02216

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>ARRANZ F ET AL: "ADDUCTS OF SUCCINYLATED DEXTRAN-BENZOCAINE. SYNTHESIS AND CONTROLLED RELEASE BEHAVIOUR" MAKROMOLEKULARE CHEMIE, RAPID COMMUNICATIONS,CH,HUTHIG UND WEPF VERLAG. BASEL, vol. 13, no. 9, 1 September 1992 (1992-09-01), pages 403-407, XP000301002 page 403, paragraph INTRODUCTION page 406</p> <p>---</p>	1-14
Y	<p>WO 95 05199 A (DEXTRAN PRODUCTS LTD) 23 February 1995 (1995-02-23) claims</p> <p>---</p>	1-14
Y	<p>SHEN ET AL: "cis-Aconityl spacer between daunomycin and macromolecular carriers: a model of pH-sensitive linkage releasing drug from a lysosomotropic conjugate" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS,US,ACADEMIC PRESS INC. ORLANDO, FL, vol. 102, no. 3, 15 October 1981 (1981-10-15), pages 1048-1054, XP002114459 ISSN: 0006-291X abstract page 1049</p> <p>---</p>	1-14
P,X	<p>HRECZUK-HIRST D.H. ET AL: "Synthesis and characterisation of dextrin-doxorubicin conjugates: A new anticancer treatment" PROCEEDINGS OF THE CONTROLLED RELEASE SOCIETY, 1999, VOL. -, NO. 26, PAGE(S) 1086-1087, XP001002321 United States page 1087</p> <p>-----</p>	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/02216

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9856424 A	17-12-1998	AU 8025998 A EP 0998303 A	30-12-1998 10-05-2000
EP 0477931 A	01-04-1992	DE 69103503 D DE 69103503 T JP 5009205 A US 5183883 A	22-09-1994 05-01-1995 19-01-1993 02-02-1993
WO 9635720 A	14-11-1996	IT PD950090 A AU 695512 B AU 5894496 A DE 69603721 D DE 69603721 T EP 0827514 A JP 11504668 T US 6017901 A AT 183206 T CA 2220682 A ES 2137694 T	11-11-1996 13-08-1998 29-11-1996 16-09-1999 13-01-2000 11-03-1998 27-04-1999 25-01-2000 15-08-1999 14-11-1996 16-12-1999
WO 9505199 A	23-02-1995	NONE	